Research Summary

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1 Extracellular Matrix (ECM)

For an extensive overview, see [4].

- The ECM constitutes the non-cellular parts of all tissues.
- It consists of:
  - Fibrous proteins, most importantly collagen, elastin and fibronectin.
  - Up to 30% collagen. Forms fibrils and fibers of different sizes which can "stick together" to make up networks. There are a bunch of different collagen types.
  - Proteoglycans, which fill the interstitial space in the form of a hydrated gel.
- Cells move through and remodel their ECM, which in turn changes their behavior.
  $\Longrightarrow$ *in silico* models need to take this into account.
- Different tissues have different ECMs.

1.1 Properties of the Extracellular Matrix

Our approach takes a macroscopic view of the ECM. Individual fibrils/fibers should not be modeled. Nevertheless we include some microscopic properties.

- **Stiffness**: Matrix stiffness has an effect on tumor gowth, e.g. [11]. Measured using Young's modulus/elastic modulus E which is given in GPa.
- **Viscoelasticity**: Creep, Stress relaxation (see below), E, η
- **Pore size**
- **Density**

[4] mentions Matrigel™ and collagen type I gels, so we will focus on these.

1.2 Viscoelasticity

What is viscoelasticity? Show some graphs and "oral" explanation

Generally modeled using differential equations involving the elastic modulus E, viscosity η, stress σ and strain ϵ. [15] mentions these constitutive models:

- Maxwell: A Viscous flow on the long timescale, but additional elastic resistance to fast deformations (e.g. silly putty, warm tar). Does not describe creep or recovery.
- Kelvin-Voigt: Does not describe stress relaxation.
- Zener/Standard linear solid: Models creep and stress relexation.

The Lethersich and Jeffreys models are models for viscoelasticity that specifically model fluids.

1.3 Rheology and Materials Science of the ECM

E.g. [18, 5]

2 Cellular Potts Model (CPM)

cites

- The CPM is a grid-based Monte-Carlo simulation for cells.
- Each cell consists of many voxels. These voxels contain its cell ID.
- In each Monte-Carlo Step (MCS), a random voxel copies the cell ID of its neighbor.
- The hamiltonian H gives the energy of a generation. It depends on the volume and surface of cells and their reciprocal adhesion.
- A MCS is always accepted if it reduces H. If it does not reduce H, it is accepted probabilistically.

3 NAStJA & CiS

- Neoteric Autonomous Stencil code for Jolly Algorithms (NAStJA) is a massively parallel stencil code solver based on OpenMPI [2].
- Cells in Silico (CiS) is an implementation of the CPM in NAStJA [3, 8].

4 Lattice Models of Viscoelastic Materials

4.1 Lattice Boltzmann Model (LBM)

- A general-purpose model of hydrodynamics discrete in time and space.
- Discretisation in space makes it possible to calculate LBM time steps using stencil codes.
- Extensive literature exists including implementation details, e.g. [10]
- Can be used to model viscoelasticity, e.g. [6, 13, 9]

5 ECM Models in the CPM

Reviews: [12, 7]

Elaborate a bit

5.1 ECM as a Cell

- Simple idea: Model ECM as a special cell, i.e. a set of voxels.
- Set properties of the ECM "cell" such that the model makes sense.
- Can model simple interactions such as matrix decomposition and deposition
- Can't really model matrix strains and deformation

E.g. [16, 17, 8]

5.2 Substrate Strain FEM

[14]

5.3 Discrete Fiber Networks

expand

See papers cited in [7], e.g. [1].

5.4 Molecular Dynamics Bead-Chain Model

[19]

6 Glossary

Acronyms

CiS Cells in Silico. 2

CPM Cellular Potts Model. 2, 3

ECM Extracellular Matrix. 1–3

FEM Finite Element Method. 3

LBM Lattice Boltzmann Model. 2

MCS Monte-Carlo Step. 2

NAStJA Neoteric Autonomous Stencil code for Jolly Algorithms. 2

References

[1] Abhilash, A. S., Baker, B. M., Trappmann, B., Chen, C. S., and Shenoy, V. B. Remodeling of fibrous extracellular matrices by contractile cells: Predictions from discrete fiber network simulations. *Biophysical Journal 107* (10 2014), 1829–1840. Focuses on "pulling" effects.

[2] Berghoff, M., Kondov, I., and Hotzer, J. Massively parallel stencil code solver with autonomous adaptive block distribution. *IEEE Transactions on Parallel and Distributed Systems 29* (10 2018), 2282–2296.

[3] Berghoff, M., Rosenbauer, J., Hoffmann, F., and Schug, A. Cells in silico-introducing a high-performance framework for large-scale tissue modeling. *BMC Bioinformatics 21* (10 2020).

[4] Frantz, C., Stewart, K. M., and Weaver, V. M. The extracellular matrix at a glance, 12 2010.

[5] Gautieri, A., and Buehler, M. J. Multi-scale modeling of biomaterials and tissues. *CISM International Centre for Mechanical Sciences, Courses and Lectures 546* (2013), 13–55.

[6] Giraud, L., D'Humières, D., and Lallemand, P. A lattice boltzmann model for jeffreys viscoelastic fluid. *Europhysics Letters 42* (6 1998), 625.

[7] Guo, Y., Mofrad, M. R. K., and Tepole, A. B. On modeling the multiscale mechanobiology of soft tissues: Challenges and progress. *Biophysics Reviews 3* (9 2022), 031303. Another review containing a bunch of nice references. Kind of hard to pull apart though since its very dense in information.

[8] Herold, J., Behle, E., Rosenbauer, J., Ferruzzi, J., and Schug, A. Development of a scoring function for comparing simulated and experimental tumor spheroids. *PLoS Computational Biology 19* (3 2023).

[9] Ispolatov, I., and Grant, M. Lattice boltzmann method for viscoelastic fluids. *Physical Review E 65* (5 2002), 056704.

[10] Krüger, T., Kusumaatmaja, H., Kuzmin, A., Shardt, O., Silva, G., and Viggen, E. M. The lattice boltzmann method. *Springer International Publishing 10* (2017). https://github.com/lbm-principles-practice.

[11] Levental, K. R., Yu, H., Kass, L., Lakins, J. N., Egeblad, M., Erler, J. T., Fong, S. F., Csiszar, K., Giaccia, A., Weninger, W., Yamauchi, M., Gasser, D. L., and Weaver, V. M. Matrix crosslinking forces tumor progression by enhancing integrin signaling. *Cell 139* (11 2009), 891–906.

[12] Liedekerke, P. V., Palm, M. M., Jagiella, N., and Drasdo, D. Simulating tissue mechanics with agent-based models: concepts, perspectives and some novel results. *Comp. Part. Mech 2* (2015), 401–444. Overview over ECM models.

[13] Malaspinas, O., Fiétier, N., and Deville, M. Lattice boltzmann method for the simulation of viscoelastic fluid flows. *Journal of Non-Newtonian Fluid Mechanics 165* (12 2010), 1637–1653.

[14] Rens, E. G., and Merks, R. M. Cell contractility facilitates alignment of cells and tissues to static uniaxial stretch. *Biophysical Journal 112* (2 2017), 755–766.

[15] Roylance, D. Engineering viscoelasticity. *Department of Materials Science and Engineering–Massachusetts Institute of Technology, Cambridge MA 2139* (2001), 1–37.

[16] Rubenstein, B. M., and Kaufman, L. J. The role of extracellular matrix in glioma invasion: A cellular potts model approach. *Biophysical Journal 95* (12 2008), 5661–5680. 1 Type for Stroma, 1 Type for Collagen¡br/¿¡br/¿Initial experiments: Static ECM¡br/¿¡br/¿Then: ECM dissolution/deposition¡br/¿Not aligned with in vivo results¡br/¿Posits idea: Simulate more than two types of matrix.

[17] Scianna, M., Preziosi, L., and Wolf, K. A cellular potts model simulating cell migration on and in matrix environments. vol. 10, pp. 235–261.

[18] Sherman, V. R., Yang, W., and Meyers, M. A. The materials science of collagen. *Journal of the Mechanical Behavior of Biomedical Materials 52* (12 2015), 22–50.

[19] Tsingos, E., Bakker, B. H., Keijzer, K. A., Hupkes, H. J., and Merks, R. M. Modelling the mechanical cross-talk between cells and fibrous extracellular matrix using hybrid cellular potts and molecular dynamics methods. *bioRxiv* (7 2022), 2022.06.10.495667.